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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,476	CANTOR, THOMAS L.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,13,14 and 17-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,13,14 and 17-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06 March 2008 has been entered.

Status of Application, Amendments and/or Claims

Applicant's arguments submitted 06 March 2008 have been entered in full. Claims 1-7, 13, 14 and 17-23 are pending and under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 13, 14, 17-23 remain rejected under 35 U.S.C. 103(a) as being unpatentable over John et al., (The Journal of Clinical and Endocrinology & Metabolism, Vol. 84, No. 11, pages 4287-4290, 1999) in view of Hutchison et al. (reference of

record, WO 03/003986 A2). The basis for this rejection is set forth at pages 2-5 of the previous Office Action (06 November 2007).

John et al. teach that excess amounts of parathyroid hormone (PTH) fragments are retained in patients with renal failure, which makes it difficult to interpret PTH measurements obtained with radioimmunoassay that use antisera directed against epitopes within the mid or carboxyl terminal regions of PTH. John et al. teach the results of PTH measurements using two different immunoradiometric assays (IRMA) in serum samples. John et al. teach a characterization specificity assay for two antibodies (N-IRMA and S-IRMA). John et al. teach a competition assay wherein radiolabelled N-IRMA antibody or radiolabelled S-IRMA antibody is incubated with hPTH(1-84) peptide. Increasing concentrations of hPTH(1-34) peptide or hPTH(2-34) peptide are then added and competition binding is assessed. It is noted that hPTH(1-84) peptide would meet the limitation of the target protein or peptide because the claim recites, "wherein target protein or peptide comprises PTH(1-34)". hPTH(1-84) comprises residues 1-34 of hPTH.

John et al. teach that the specific binding of radiolabelled N-IRMA antibody to hPTH(1-84) peptide was progressively and equally reduced by increasing concentrations of hPTH(1-34) peptide and hPTH(2-34) peptide. ***In contrast,*** the S-IRMA radiolabelled antibody binding was reduced by hPTH(**1**-34) peptide, ***but not by*** hPTH(**2**-34) peptide (page 4289, Figure 3). This would mean that the S-IRMA antibody is specific for the 1st amino acid in hPTH because the only difference between the hPTH(**1**-34) peptide and the hPTH(**2**-34) peptide is the 1st amino acid. Thus, John et al.

teach an antibody that binds to a target protein/peptide containing a specific amino acid residue (i.e. hPTH 1-34) but fails to bind to negative protein/peptide (i.e. hPTH 2-34). The target protein/peptide comprises PTH(1-34) and the negative protein/peptide comprises PTH(2-34) and lacks the first amino acid residue of PTH and said specific amino acid is the first amino acid residue of PTH**.** John et al. teach that the results indicate that the S-IRMA antibody selectively detects human PTH with an intact amino-terminus (i.e. a specific amino acid residue dependent antibody, which targets PTH1-34)(Discussion)(**applies to claims 1, 5-7**). John et al. do not teach immunizing a mammal with an immunizing protein or peptide comprising target protein or peptide or purifying an antibody from a mixture of antibodies.

Hutchison et al. teach monoclonal or polyclonal antibodies which recognize PTH (page 1 and page 19, lines 22-35). Hutchison et al. teach that the antibodies will recognize an amino acid sequence from position 1-13 of PTH or combinations thereof or in regions consisting of amino acids 14-84 or 13-34 (page 16). The PTH antibodies are produced by immunizing animals with intact PTH, variants thereof, or mixtures thereof (page 17, lines 15-32 and page 29, lines 11-32). The PTH antibodies are isolated by exposing sera to antibody affinity purification columns. Solid columns are linked with various PTH peptides, including hPTH amino acid residues 1-13, 13-34 and 39-84 (page 18, lines 15-34 and page 30). Hutchison et al. teach an assay wherein an antibody is immobilized on a solid phase (capture antibody), incubated with an antigen, and further incubated with an antibody with a detectable label (detection antibody) (page 20). Hutchison et al. teach that an antigen can be immobilized on a solid phase

incubated with a diluted antiserum or a purified antibody and detectable label, thereby obtaining a labeled binding substance. Hutchison et al. teach a method wherein an antibody is labeled with a detectable label and the other antibody is allowed to bind to a solid phase as a solid phase antibody or is made to be able to specifically bind to a solid phase (capture antibody). The antibodies are allowed to react with antigens in various concentrations to form a plurality of antigen-antibody complexes. Since the antigen-antibody complexes are solid phases, the solid phases are separated from the complexes, and the amount of label in the solid phases is measured. The relationship between the label and the concentration of the antigen is plotted to obtain a standard curve (page 21). Hutchison et al. teach the isolation of antibodies to PTH1-13. Each of the PTH peptides (1-12, 13-34, 38-84) was coupled to sepharose. Goat immune serum was sequentially purified on the affinity columns to first remove anti-PTH38-84 antibodies, then anti-PTH13-34 and then anti-PTH1-13 antibodies (pages 30-31). Hutchison teaches that anti-PTH1-13 antibodies are labeled for detection and anti-PTH39-84 antibodies are labeled for capture. Hutchison et al. teach that the capture and detection antibodies sandwich the PTH molecules in the sample. The sandwich complex is bound to streptavidin-coated magnetic particles. Hutchison teaches the inhibition of certain PTH peptides (page 33, lines 24-33; page 35, lines 19-29 and page 36, lines 4-19).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify a method of identifying a specific amino acid residue dependent antibody to target PTH as taught by John et al., by immunizing a mammal

with an immunizing PTH peptide and purifying a PTH antibody from a mixture of antibodies (antisera), as taught by Hutchison et al. with a reasonable expectation of success. The motivation and expected success is provided by John et al., who identify the S-IRMA antibody which specifically detects full length human PTH, but no truncated fragments and the general knowledge to one of skill in the art that antibodies are made by immunizing a mammal (with a specific peptide) and then purifying it from a mixture of antibodies (i.e. sera).

Applicant argues that John et al. do not describe a method for identifying antibody S-IRMA. Applicant argues that unlike an anticipation rejection, where the characteristics of the S-IRMA antibody might be relevant, the properties of that antibody are not relevant to the obviousness analysis unless they provide a reason to identify the antibody according to the present claims. Applicant argues that the S-IRMA antibody is a composition and its properties have nothing to do with the method claims. Applicant maintains that a composition does not render obvious all methods for its preparation. Applicant argues that John et al. appears to use PTH(1-34) and PTH(2-34) solely as a test of how they affect binding between S-IRMA antibody and PTH(1-84), but that does not disclose or suggest an antibody according to the claim, and it does not provide motivation for a person of ordinary skill to identify such an antibody. Applicant argues that the John et al. reference does not disclose the step of assessing binding between said antibody and said target binding protein or peptide and assessing binding between said antibody and negative screening protein or peptide. Applicant maintains that even if the S-IRMA antibody was contacted with PTH(1-34) and PTH(2-34), it was not done to

asses the binding of the antibody to PTH(1-34) or PTH(2-34), only to assess whether those peptides interfere with S-IRMA antibody's binding interaction with PTH(1-84). Applicant argues that the passage that the rejection relies upon merely says, "the S-IRMA antibody binding was reduced by hPTH(1-34), but not by hPTH(2-34)". Applicant maintains that this passage does not describe assessing the binding of the S-IRMA antibody to PTH(1-34), or assessing the binding of an antibody to PTH(2-34), only the binding of an antibody to PTH(1-84) and how/whether that binding is affected by the presence of other peptides. Applicant argues that John et al. do not assess the binding of an antibody to those two peptides as required by the claimed method, since the assay John et al. use is designed to form a sandwich complex that apparently depends on the C-terminal portion of PTH. Applicant argues that if the sandwich assay detected the PTH(1-34) and/or PTH(2-34) that was added in the competition experiments, they would increase the amount of radiolabelled complex formed rather than reducing it by interfering. Applicant argues that neither John nor Hutchison discloses a reason to identify an antibody having a PTH(1-34) peptide as its target, with selectivity over a PTH(2-34) peptide. Applicant argues that neither of the two references was shown to provide motivation to identify an antibody having the characteristics required by the antibody that claim 1 seeks to identify, since they do not provide a reason to produce such an antibody. Applicant argues that claim 17 is directed to a method that is designed to provide an antibody that targets PTH(1-34) without binding to PTH(2-34) and since the references do not provide motivation for one of ordinary skill to pursue that antibody, this method claim is not rendered obvious by the cited references.

Applicant's arguments have been fully considered but are not deemed persuasive. John et al. clearly teach that excess amounts of PTH fragments are retained in patients with renal failure and this has made it difficult to interpret PTH measurements using conventional radioimmunoassays, which use antisera directed against epitopes within the mid- or carboxy terminal region of PTH. John et al. clearly try to identify an antibody which would identify the full-length human PTH by examining the N-IRMA and the S-IRMA antibody in a binding assay. John et al. clearly teach that the results indicate that the S-IRMA selectively detects human PTH with an intact amino-terminus.

Contrary to Applicant's assertion, competition binding assays are used to assess specific binding of antibodies to target proteins. John et al. teach a competition assay wherein radiolabelled S-IRMA antibody is incubated with hPTH(1-84) peptide. Increasing concentrations of hPTH(1-34) peptide or hPTH(2-34) peptide are added. If hPTH(1-34) peptide or hPTH(2-34) peptide is able to compete away the S-IRMA antibody from its binding/incubation with hPTH(1-84) peptide, one would see a decrease in S-IRMA binding. Figure 3, panel B shows that hPTH(1-84) peptide is able to compete S-IRMA antibody from its binding/incubation with hPTH(1-84) peptide. Figure 3, panel B, small inset shows that hPTH(**1**-34) peptide is able to compete S-IRMA antibody from its binding/incubation with hPTH(1-84) peptide. *However*, hPTH(**2**-34) peptide was not able to compete S-IRMA antibody from its binding/incubation with hPTH(1-84) peptide. This would mean that S-IRMA is specifically targeting the 1st amino acid in hPTH because the only different between the hPTH(**1**-34) peptide and the

hPTH(**2**-34) peptide is the 1st amino acid. John et al. employed a method to identify a specific amino acid residue dependent antibody. John et al. identified the S-IRMA antibody as an antibody which recognizes the 1st amino acid in the amino-terminal region. This was done by employing a method which contacted an antibody (i.e. N-IRMA or S-IRMA) with a target protein or peptide (i.e. hPTH1-84) and a negative screening protein or peptide (i.e. hPTH2-34) and assessing binding between the antibody and target protein or peptide and assessing binding between the negative screening protein or peptide. As was stated above, hPTH(1-84) peptide meets the limitation of a target protein or peptide comprising PTH(1-34).

The instant claims are drawn to a method of screening for a specific amino acid residue dependent antibody to target a protein/peptide comprising PTH(1-34) and methods of making said antibody. John et al. teach the importance of identifying an antibody which specifically detects full length human PTH. John et al., by employing a binding competition assay, identifies the S-IRMA antibody. Hutchison teach various methods of immunizing animals, making and purifying PTH antibodies. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the

grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

RMD
4/17/08